Dennis M. Erb, Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Tel 610 397 7597
215 652 5000
Fax 610 397 2516

February 4, 2000

7610 '00 FEB -8 A9:57

MERCK
Research Laboratories

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive Room 1-23
Rockville, MD 20857

Docket No. 99D-5047
Draft Guidance: Pharmacokinetics in Patients with Impaired Hepatic Function: Study, Design, Data Analysis, and Impact On Dosing & Labeling

Merck & Co., Inc., is a worldwide research-intensive company that leads the ethical U.S. pharmaceutical industry in discovery, development, production and marketing of human and animal health products and specialty chemicals. Merck Research Laboratories (MRL), Merck's research division, is one of the leading biomedical research organizations dedicated to improving human health, animal health, and agriculture. Through a complex and multidisciplinary process, MRL involves scientists from every technical discipline in targeting, discovering, and testing compounds to conquer today's unique diseases. MRL's innovation strategy includes research and development of many compounds or potential drug candidates at one time.

Today's R&D is a highly risk-intensive worldwide business. Commercialization of products in many countries directly depends upon regulatory climates that foster timely development and government policies that are consistent and socially responsible, but do not add extra uncertainty to the research and development process. Indeed, we are also concerned about inconsistencies among regulatory regimes in different countries that may require unusual or duplicative research testing.

For these reasons, we are very interested in and well qualified to comment on this FDA proposal to provide guidance on study design, data analysis, and potential impact on labeling of pharmacokinetic studies in patients with impaired hepatic function. Following are specific comments and recommendations to enhance the development of the subject guidance.

99D-5047

C6

SPECIFIC COMMENTS:

Page 4, A. 1. Study Participants, Para. 3

The Draft Guidance states: " *... a reduced study design involving control subjects and patients with a Child-Pugh category of moderate impairment would generally be sufficient. Under these circumstances, the findings in the moderate category will be applied to the mild category and dosing in the severe category would be generally contraindicated".*

If there is no clinically important effect of moderate impairment on pharmacokinetics, this approach is very suitable. However, if there is a clinically important effect of moderate impairment on pharmacokinetics, it would be preferable to have the option for directly studying the category with mild impairment to assess explicitly if the same or different result (and labeling statement) would apply to mild and moderate categories.

Page 5, A.3. Sample Collection and Analysis

The Draft Guidance states: *"For drugs that are highly extracted by the liver (extraction ratio > 0.7) and that are extensively bound to plasma proteins (fraction unbound* **< 20 %)**, *the unbound fraction should be determined at least at trough and maximum plasma concentration."*

We suggest that fraction unbound **< 10 %** is a more appropriate boundary to describe drugs that are extensively bound to plasma proteins and would require measurement of unbound drug. Monitoring unbound fraction at the maximum plasma concentration is certainly appropriate in such a situation. Of course, monitoring unbound fraction at trough may be technically difficult in many circumstances due to assay sensitivity issues, and perhaps the Guidance should acknowledge this. Additionally, we suggest that the request to measure unbound drug should apply to oral drugs only. For intravenous administration of drugs with high hepatic extraction, clearance is approximated by hepatic blood flow, and there should be no effect of protein binding.

Page 7, V.A. Parameter Estimation

The Draft Guidance states: "*Plasma concentration data (and urine concentration data, if collected) should be analyzed to estimate measurements and/or parameters describing the PK of the drug and its active metabolites (e.g., area under the plasma concentration curve (AUC), peak concentration (Cmax), apparent clearance (CL/F), renal and nonrenal clearance (CLR and CLNR), apparent volume of distribution (Vdz or Vdss), terminal half-life (t1/2)). Where relevant, measurements and/or parameters may be expressed in terms of unbound concentrations (e.g., apparent clearance relative to the unbound drug concentration (Clu/F=Dose/AUCu, where the subscript u indicates unbound drug)). Noncompartmental and/or compartmental modeling approaches to parameter estimates can be used."*

We suggest it be stated more explicitly that AUC will typically be the primary parameter of interest, Cmax typically the secondary parameter of interest, and other parameters typically exploratory. Obviously, not every parameter will be obtained for every compound. For example, nonrenal clearance will not be calculable for an orally administered compound.

Page 8, V.C. Development of Dosing Recommendations; 2nd Bullet

The Draft Guidance states: *"If the sponsor wants to claim no effect of hepatic impairment on the drugs PK, then one of the following criteria should be established: (1) delineation of no effect boundaries prior to conducting the studies, based on information available for the investigational drug (e.g., dose- and/or concentration-response studies); (2) in the absence of other information to determine a different equivalence interval, a standard 90 percent confidence interval of 80-125 percent for AUC and 70-143 percent for Cmax can be used for the investigational drug."*.

We agree with this general approach, but have some suggestions with regard to the details. The Draft Guidance goes on to state *"Given the small numbers of subjects usually entered into hepatic impairment studies, FDA recognizes that documentation that a PK parameter remains within a certain no effect boundary at a certain level of confidence is unlikely"*, and thus the Agency implicitly acknowledges that the meeting the standard of bioequivalence is generally an impractical boundary for studies of this nature which generally have small numbers of patients. We appreciate having the first option to define other boundaries: "*delineation of no effect boundaries prior to conducting the studies, based on information available for the investigational drug*". But this is generally difficult to do in a definitive sense prior to integrated review of Phase I, II and III safety and efficacy data to define the therapeutic index.

We propose that at the time of initiation of the hepatic impairment PK study, a tentative 90 percent confidence interval for no clinically important effect be stated in the protocol, based on the data available at that time. We further propose that at the time of integrated review of all Phase I, II and III safety and efficacy data (e.g. in the WMA), the Sponsor provide further data to support or refine this tentative 90 percent confidence interval for no clinically important effect, and if the interval has changed, repeat the statistical analysis to support the final determination of whether there are clinically important effects and the corresponding labeling recommendations. Obviously, this issue transcends consideration of hepatic insufficiency per se and parallel approaches could be used for the other types of pharmacokinetic studies.

Page 10, A.I. Pharmacokinetics, 2nd and 3rd bullets

The Draft Guidance states that for labeling the Clinical Pharmacology section should include information on:

- *Percent of drug eliminated by the liver*
- *Disposition of metabolites in patients with impaired hepatic function (if applicable)*

We presume that "percent of drug eliminated by the liver" is operationally defined as "percent of drug eliminated by non-renal clearance" for an intravenous drug. For an orally administered drug, the closest approximation to hepatic clearance typically is the percent of a radiolabeled dose excreted as radioactivity in the feces. Obviously, this includes unabsorbed drug as well as products of hepatic metabolism. We suggest that the Guidance acknowledge these limitations in quantitating the percent of drug eliminated by the liver.

Additionally, when the Draft Guidance states "disposition of metabolites.....(if applicable)", we presume "if applicable" refers to a major, pharmacology active metabolite(s), just as earlier at several points in the Draft Guidance, all references to PK assessment of metabolites refer only to active metabolites.

Page 13, V.I.C. Dosage and Administration Section

The Draft Guidance states: *"The influence of impaired hepatic function on _____pharmacokinetic or pharmacodynamics (if known) is sufficiently small that no dosing adjustment is required".*

This type of information is usually not added to the Dosage and Administration section of the package circular when no dosage adjustment is required. To add it for the hepatically impaired population might result in having to add similar statements for other populations studied for which there are no reasons to adjust dosage. Thus, making the section longer than necessary and more difficult to find the appropriate information for populations that do need dosage adjustment. We propose a revision to the guidance stating that changes to the Dosage and Administration section are only necessary when dosage adjustments are recommended.

We appreciate the opportunity to comment on this draft guidance and hope our comments and recommendations are considered in writing the final version.

Sincerely,

Dennis M. Erb

Dennis M. Erb, Ph.D.
Senior Director
Regulatory Affairs

Q/ligi/guidance/99D5047